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Six Patients With Oral-Facial-Digital Syndrome IV: The Case for Heterogeneity

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The oral-facial-digital syndromes (OFDS) have in common minor facial and oral anomalies (including tongue lobulation and/or hamartomas, accessory frenula, and alveolar anomalies) and variable digital defects such as polydactyly. The classification based on the presence of additional findings [Toriello, 1988, 1993] is not perfect, as many reported examples of a particular OFDS have some other condition. Here we describe six children, all diagnosed as having OFDS IV (OFDS with tibial defects), whose manifestations illustrate the apparent genetic heterogeneity. Am. J. Med. Genet. 69:250–260, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: limb defects; multiple congenital anomaly syndrome; autosomal recessive inheritance

INTRODUCTION

In 1954, Papillon-Leage and Psaume described an X-linked dominant entity they termed oral-facial-digital syndrome (OFDS). This report was preceded by the description of Mohr [1941] of a distinct oral-facial-digital syndrome, which ironically became known as OFDS II [Rimoin and Edgerton, 1967]. Subsequently, additional OFDS were reported, with the delineation of at least nine distinct OFDS by 1993 [Toriello]. There are descriptions of other conditions that may be considered OFDS, but are less well defined and/or not classified.

Recently we evaluated six children with a diagnosis of OFDS IV (oral-facial-digital syndrome with tibial defects), who clearly have different conditions. We review OFDS IV to determine the extent of heterogeneity that exists within this OFDS subtype.

CLINICAL REPORTS

Patient 1

This boy was born at term after an uncomplicated pregnancy to a G2, P2 mother and her nonconsanguineous husband. The older brother is healthy and has no anomalies. Birthweight was 4.28 kg, length 56.5 cm, and OFC 42.5 cm (all > 95th centile). Because of his large head size, CT scanning was done, and large frontal and posterior fossa cysts were found. The ventricles were not seen, and it was suspected that they had collapsed. Shunts were subsequently placed. In addition he had an asymmetric face, epicanthal folds, hypertelorism, depressed nasal bridge, short nose with anteverted nares, flat philtrum, and micrognathia. The palate was highly arched, and there were hyperplastic frenula between the lower lip and alveolar ridge. The left ear was apparently lowset and posteriorly angulated.

Hand anomalies included bilateral soft tissue syndactyly between the 4th and 5th digits and postaxial polydactyly (Fig. 1). The great toes were duplicated; the left leg was 2 cm shorter than the right. The left foot was in the varus position (Fig. 2). The middle phalanx of each fifth finger and the middle phalanx of the right index finger were hypoplastic. The left femur had mild anterior and lateral bowing and was shorter than average. The left tibia was bowed and short and showed mild irregular cortical thickening along the lateral and posterior aspects. There were two distal phalanges in the right great toe and three distal phalanges in the left. There was one proximal phalanx bilaterally. There was also a rudimentary extra metatarsal on the left, whereas the first metatarsal was irregular and broad. Other than craniofacial disproportion, the skull and trunk were considered normal. Chromosomes and results of TORCH screen were normal.

Since infancy the child has had frequent upper respiratory infections. He has had bilateral inguinal her-

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Fig. 1. Patient 1, polydactyly.

niae repairs and has developed seizures characterized by periods of tachypnea and occasional apnea. Results of hearing tests have been normal; the child is severely mentally retarded.

Over time, the facial appearance has become more striking, with more apparent asymmetry and nasal alar hypoplasia (Fig. 3). The leg asymmetry is also more striking, with all long bones of the left leg shorter than those of the right.

Fig. 2. Patient 1, note preaxial polydactyly of patient's left foot.

Fig. 3. Patient 1, note facial asymmetry and alar hypoplasia.

Patient 2

This male was seen at the age of 7 years for a brief evaluation. A diagnosis of Ellis-Van Creveld syndrome had been made elsewhere. He was short (105 cm), had macrocephaly (OFC 57 cm, > 97th centile), sparse scalp hair, dolichocephaly, telecanthus, broad nasal tip, repaired midline cleft of upper lip, oral frenula, hamartoma of the tongue dorsum, diastema of upper incisors, alveolar cleft of lower gum (Fig. 4), absent mandibular central incisors, brachydactyly with postaxial polydactyly (repaired) of the fingers, and history of genitourinary anomalies. Roentgenographs from early infancy demonstrated short tibiae but with shorter fibulae (Fig. 5), rounded metaphyses of tibiae, short broad ilia

Fig. 4. Patient 2, note midline cleft lip, lower alveolar cleft.

Fig. 5. Patient 2, note short fibula.

with small sacro-iliac notch, and fusion of the fourth and fifth metacarpals of one hand.

Patient 3

This girl was the third child born to Mexican-Native-American parents. Maternal and paternal age was 19 and 24 years, respectively. Consanguinity was denied. However, the parents are from a small village with little population mobility. The two older children are normal boys. Pregnancy was uneventful. The mother denied use of drugs other than prenatal vitamins. Birthweight was 3,800 g at term. No other birth information is available. The child was brought to the United States for treatment of "club feet."

At 3 weeks of age the child had multiple congenital anomalies and episodes of cyanosis and difficulty in feeding and handling oral secretions. Head circumference was 35.5 cm (50th centile). The anterior fontanel was soft, open, and flat. The anterior hairline was low. There was dystopia canthorum and zygomatic hypoplasia with one milia spot anterior to the right ear. She had a small mouth with downturned corners. A small

Fig. 6. Patient 3, note preaxial and postaxial polydactyly.

pseudocleft was present in the midline of the upper lip. The palate was highly arched with a small leftsided cleft of the soft palate and bifid uvula. The tongue was short with multiple frenula causing excessive ankyloglossia. Sublingual white-colored hamartomas were present. The mandible was small. A left supernumerary nipple was present. All four limbs had preaxial or postaxial polydactyly and syndactyly (Figs. 6 and 7), with mesomelic shortness of the lower limbs and bilateral talipes equinovarus.

Fig. 7. Patient 3, note preaxial and postaxial polydactyly.

Fig. 8. Patient 3, age 1 year. Note facial appearance.

Fig. 9. Patient 4, note facial appearance, including small midline cleft upper lip.

At 6 weeks of age, there were poor startle, Moro, grasp, and rooting reflexes. Sucking was considered weak and inefficient. The child had poor head control, did not reach, and tracked inconsistently. Muscle tone fluctuated between hypo-and hypertonia. Auditory brainstem-evoked potentials showed significant auditory defect on the right. At 1 year, the patient had marked psychomotor delays. Phenotype was unchanged (Figs. 8 and 9). Cranial radiographs demonstrated hypoplastic frontal sinuses, sphenoid, and zygomatic bones. The sella was "J" shaped.

The infant had seven digits bilaterally with pre-and postaxial polydactyly and syndactyly of the first two digits. The first two digits on the left had one proximal and two distal phalanges; on the right there were two proximal and two distal phalanges. There was brachydactyly of all digits with hypoplasia of the distal phalanges and clinodactyly of the fourth and sixth digits, bilaterally. There were six metacarpals on each hand. On the left hand, the fifth and sixth metacarpal bones were joined proximally.

Lower limb roentgengraphs showed shortness of the tibiae and fibulae with the fibula longer than the tibia. The proximal metaphyses of the tibiae and femora were rounded in appearance. Irregular ossification of the epiphyses of the proximal femurs could be seen. Bilateral talipes equinovarus was present. There were seven toes bilaterally with duplication of the great and small toes and soft tissue syndactyly of all digits. Seven metatarsals were present. The duplicated first two metatarsals were short and broad. The terminal phalanges of the toes were poorly ossified.

Cranial CT scan performed at 3 months, without contrast, showed normal ventricles. A slight delay in gray-white matter differentiation was noted. Renal ultrasound findings were normal.

Patients 4 and 5

Patient 4, a boy, was born at 38 weeks, with birthweight of 2.2 kg (< 5th centile), length of 48 cm (50th centile), biparietal fullness, upturned nose (Fig.9), small cleft tongue with nodules, irregular alveolar ridges, frenulum connecting the tongue to the mandibular alveolar ridge (Fig. 10), U-shape cleft palate, and micrognathia. Chest was narrow with a long thorax. Range of joint motion was normal. Hands were also normal, including fingers, thumbs, and nails. He had broad great toes with hypoplastic toenails and mild shortness of all limbs. Phallus appeared normal, although testes were not palpable.

Roentgenographs demonstrated short ribs (Fig. 11), hypoplasia/aplasia of toe phalanges with mild shortness of the first metatarsals and great toe phalanges, and mild shortness of the tibiae and ulnae. Cranial ultrasound showed agenesis of corpus callosum, hypoplasia of the cerebellar vermis, hydrocephalus involving the third lateral ventricles with short small Sylvian fissures and a prominent cisterna magna. CT scan

Fig. 10. Patient 4, note hyperplastic frenulae.

showed a Dandy-Walker variant with small brainstem, cerebellar hypoplasia, and cerebral atrophy.

This boy was hospitalized several times for apnea and pneumonias. A gastrostomy was placed, and later a tracheostomy was done. He developed seizures and manifested significant developmental delay. He died at age 3. Autopsy demonstrated some previously undiagnosed anomalies, including absent epiglottis, laryngeal stenosis, and laryngotracheoesophageal fistula.

One year after the boy's death, an ultrasound study done during the mother's third pregnancy at 26 weeks showed Dandy-Walker anomaly, polydactyly, and short long bones. Amniocentesis demonstrated a 46, XX normal karyotype. The pregnancy was terminated, and autopsy of the fetus (patient 5) demonstrated Dandy-Walker anomaly, absent corpus callosum, abnormal tongue and mandible, short lower limbs with club feet, polydactyly and syndactyly of toes, and malrotation of the intestine.

Fig. 11. Patient 4, note narrow chest, short appearing ribs.

Patient 6

This 10-year-old Mexican boy was born at term to first-cousin parents following an uncomplicated pregnancy. Maternal age was 31 and paternal age 29 years. An older brother was healthy, and there was one previous first trimester spontaneous abortion. Delivery was spontaneous vaginal vertex with birthweight 2.8 kg, length 48 cm, occipitofrontal circumference 33.2 cm.

Neonatally he was found to have microcephaly, synophrys with arched, upswept eyebrows, long eyelashes, marked hypertelorism and telecanthus, and short palpebral fissures. The left ear was apparently low set and posteriorly angulated and the right helix overfolded. Other facial anomalies included a broad nose with a high bridge and short columella, micrognathia, a deeply cleft central mandibular alveolus, microglossia, narrow hard palate with a posterior cleft, and absent uvula. Partial airway obstruction occurred in the supine position.

Limb anomalies included incomplete extension and supination at the elbows with deep dimples over both elbows, single transverse palmar creases bilaterally, brachydactyly with pre-and postaxial polydactyly of the hands, with the extra digits fused to the first and fifth digits, respectively, and short nails. There was marked bilateral tibial bowing (Fig. 12). He had talipes equinovarus deformities with seven toes on the right

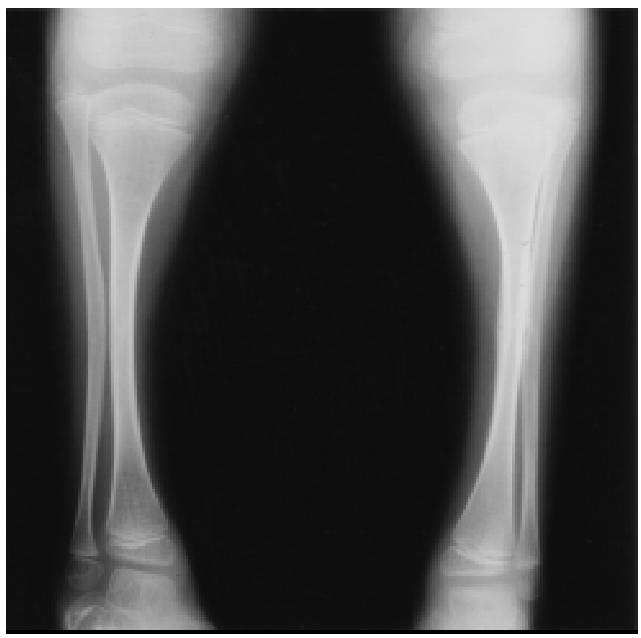

Fig. 12. Patient 6, note tibial bowing.

Fig. 13. Hand of patient 6 with preaxial polydactyly.

and eight on the left, and widely set nipples and micropenis.

A gastrostomy tube was placed at 12 days. Ophthalmologic findings were normal. An echocardiogram showed possible mild valvular pulmonic stenosis. A CT scan of the head performed at 8 days because of jerking movements of the limbs was normal, as was a repeat scan at 3 years. Roentgenographs showed hexadactyly of the left hand, with hypoplasia of the fifth finger, an abnormal thumb, polydactyly of the feet with eight toes on the left and seven toes on the right. A chest film was normal, including bony structures. Subsequent Roentgenographs demonstrated increased fibular growth compared to the tibiae. The patellae were delayed in ossification. There was diffuse osteopenia. Karyotype was normal (46,XY).

Multiple surgeries were performed, including removal of supernumerary digits of the hands and feet and repair of bilateral equinovarus deformities (Figs. 13, 14). At 10 years, he underwent epiphyseodesis and segmented resection of the proximal left fibula (see Fig 17). Facial appearance continues to be distinct, with prominent epicanthal folds, synophrys, thin alae, thin upper lip (Fig. 15), micrognathia (Fig. 16), and highly arched palate (Fig. 17).

DISCUSSION

Our patients very likely have different conditions, although all have oral, facial, digital, and tibial defects.

Fig. 14. Feet of patient 6, note polydactyly.

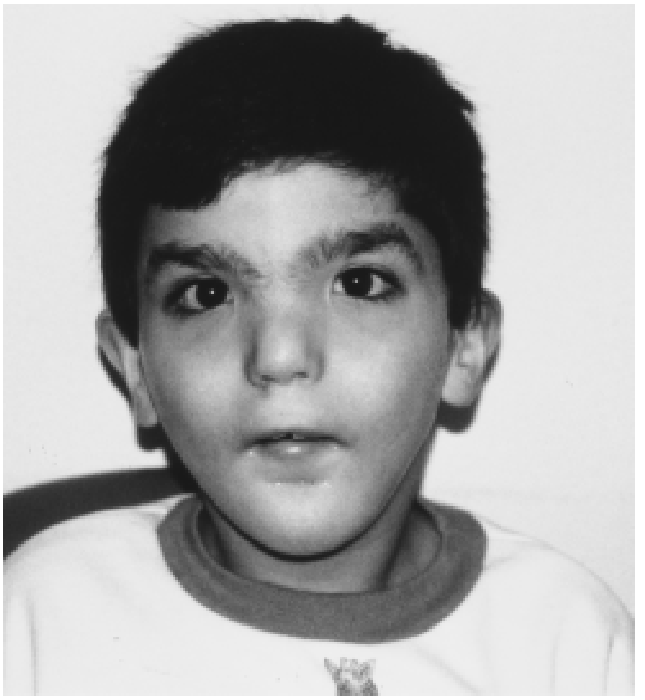

Fig. 15. Patient 6, note facial features.

Baraitser et al. [1983] first described a child with a phenotype that prompted them to suggest that the child had a Mohr-Majewski compound. Later, Burn et al. [1984] described an affected sib of the child and

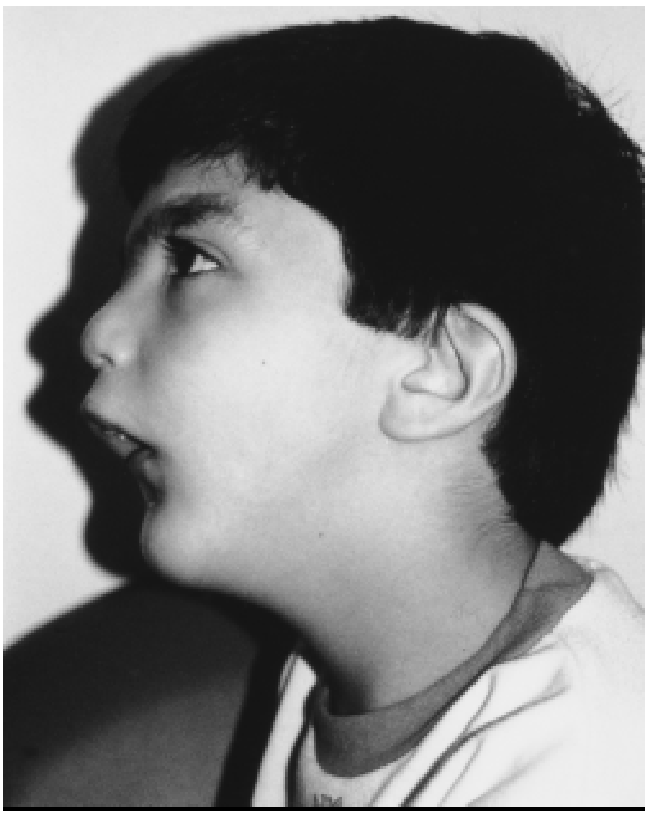

Fig. 16. Patient 6, note micrognathia.

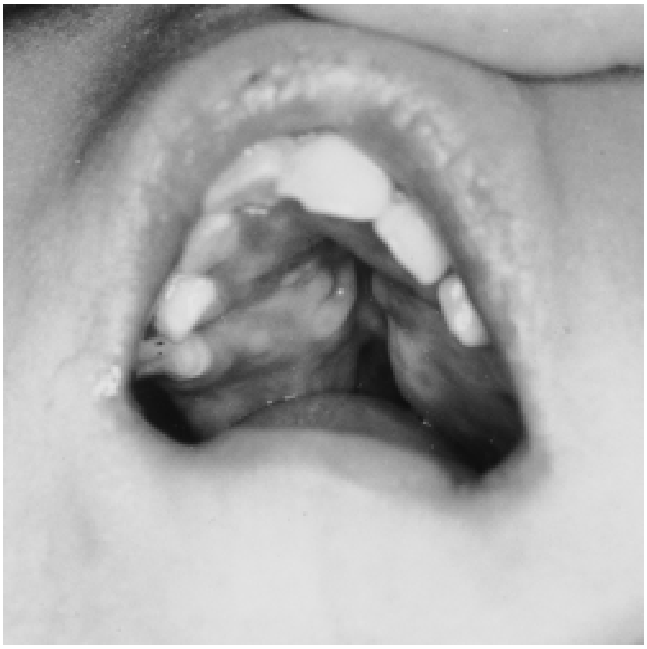

Fig. 17. Palate of patient 6.

suggested the designation OFDS IV. This publication should therefore serve as the prototype for OFDS IV, with the phenotype consisting of minor facial anomalies, oral frenula, tongue nodules with or without lobulation, digital anomalies including polydactyly, club feet, hearing loss, and long bone anomalies limited to tibial defects.

Our patients 3 and 6 are examples of this condition. Other possible examples are the patients of Rimoin and Edgerton [1967], Sugarman [1983], Goldstein and Medina [1974], Bonioli et al. [1979], and Michels et al. [1985] (Table 1). Minor differences among these patients exist, e.g., the sibs described by Rimoin and Edgerton [1967] did not have hand polydactyly, and the patient described by Sugarman [1983] did not have hearing loss and was described as having a relatively small thorax; however, these differences are probably not substantial enough to suggest heterogeneity. The consanguinity of the parents of patient 5 support autosomal recessive inheritance of type IV OFDS.

Temtamy and McKusick [1978] described a child with oral, facial, and digital anomalies in addition to skeletal defects, most notably, short arms and small thorax; this child was also reported by Sensenbrenner and Jorgenson [1975]. They used the term Mohr-Majewski compound to describe the phenotype in their patient. Preaxial polydactyly of the feet was the only digital anomaly; mild mental retardation was also present. A similar patient was described by Berberich et al. [1989], although this child also had duplication of thumbs, epiglottal anomalies, and an abnormal anus. The authors suggested that this represented a "new" OFD syndrome. A "new" OFD was also the designation given by Chitayat et al. [1992] to the phenotype in sibs who also resemble the above two patients. However, these children also had cerebellar anomalies and post-

TABLE I. Oral-Facial-Digital Syndrome IV

	Burn et al., 1984		Rimoin and Edgerton, 1967		Sugarman, 1983	Goldstein and Medina, 1974		Michels et al., 1985		Bonioli et al., 1979	Patient	Patient
	1	2	1	2		1	2	1	2		3	6
Facial												
Hypertelorism/ telecanthus	−	−	+	+	−	−	−			+	+	+
Broad nasal tip			+	+	+	+	+	+	−	+		−
Midline cleft lip	−	−	+	+	−	Right	−	±	+		+	−
Micrognathia	+	−	+	+	+	+	−	+		+	+	+
Oral												
Frenula	−	−	+	+		+	+	+			+	−
High/cleft palate	+	+	+		+	+	+	+			+	+
Tongue nodules	+	+	+	+	+	+	+	+		+	+	−
Cleft tongue	−	−	+	+		+	+			+	−	
Hand												
Syndactyly	+	+	−	+	+	−	−	+	−	+	+	−
Preaxial polydactyly	−	−	−	−	+	−	−	+	+	+	+	+
Postaxial polydactyly	+	+	−	−	+	−	−	+	+	+	+	+
Clinodactyly	−	−	+	+		+	+	+		+	+	
Foot												
Preaxial polydactyly	+	+	+	+	+	−	−	+	+	+	+	+
Postaxial polydactyly	+	+	−	−	+	−	−	+	+	−	+	+
Clubfoot	+	+	−	−	+			+	+	−	+	+
Skeletal												
Short ± bowed tibiae	+	+			+	+	+			+	+	
Wide metaphyses			+	+		+	+			+		
Other												
Deafness	+	+	+	+		+	+			−	+	−
Literature diagnosis	OFD IV	OFD IV	OFD IV	OFD IV	Unknown OFD	OFD II	OFD II	OFD II	OFD II	OFD II		
Comments	Sibs	Sibs	Sibs	Sibs		Sibs	Sibs	Sibs	Sibs			

TABLE II. Examples of Patients With Oral-Facial-Digital Syndrome With Skeletal and Visceral Defects*

	Chitayat et al., 1992		Temtamy and McKusick, 1978	Berberich et al., 1989	Nevin and Thomas, 1989			
	1	2			1	2	Patient 4	Patient 5
Facial								
Hypertelorism	+	+	+		+	+		
Broad nasal tip	+	+	+		+	+	+	
Midline cleft	–	–	+	+	+	+	–	+
Micrognathia	+	+	+		+	+	+	+
Oral								
Frenula			+	+	+	–	+	
High/cleft palate	+	+	+		+	+	+	
Tongue nodules			+		–	–	+	–
Cleft tongue	+	+	–	+	+	–	+	–
Hand								
Syndactyly	+	+	–				–	–
Preaxial polydactyly	–	–	–	+	+	+	–	–
Postaxial polydactyly	+	+	–		+	+	–	–
Foot								
Preaxial polydactyly			+	+	+	+	–	+
Postaxial polydactyly	+	+	–		+	+	–	–
Skeletal								
Narrow/small thorax	+	+	+	+	–	–	+	
Short ± bowed tibiae	+		+	+	+	+	+	+
Short arms	+	+	±	+	+	+	+	
Visceral								
Epiglottal/laryngeal				+	+	–	+	
Deafness			+	+	+			
Genital defects			+	+	–	–	+	–
Cerebral anomalies	+	+			–	–	ACC DW	ACC DW
Literature diagnosis	"New" OFD	"New" OFD	Mohr-Majewski	"New" OFD	OFD IV	OFD IV		
Comment	Sibs	Sibs					Sibs	Sibs

*ACC = agenesis of corpus callosum; DW = Dandy-Walker.

TABLE III. Examples of Patients With Oral-Facial Digital Syndrome With Lethal Outcome

	Ades et al., 1994	Meinecke and Hayek, 1990	Gillerot and Koulischer, 1988
Facial			
Hypertelorism		+	+
Midline cleft		+	+
Micrognathia	+	+	+
Oral			
Frenula		+	
High/cleft palate	+	+	+
Cleft tongue		+	
Hand			
Syndactyly	+	+	+
Preaxial polydactyly			+
Postaxial polydactyly	+	+	+
Foot			
Preaxial polydactyly	+	+	
Postaxial polydactyly	+	+	
Skeletal			
Small thorax	+	+	±
Short ± bowed tibiae	+	+	+
Abnormal ribs	+	–	–
Other			
Epiglottal/laryngeal	+	+	
Cardiac		+	+
Genital	+	+	
Renal	+	+	
Brain	+	+	+
Literature diagnosis	OFD IV	Mohr-Majewski	Mohr-Majewski
Comment	Sporadic; parents related	Sporadic	Sporadic

TABLE IV. Other Syndromes With Oral, Facial, and Digital Anomalies and Tibial Defects

Anomaly	Ellis van Creveld	C Syndrome	Robinow	Pallister-Hall	Smith-Lemli-Opitz II	Hydrolethalus	Meckel	Beemer-Langer
Oral	Maxillary frenula	Highly arched/cleft palate; maxillary frenula	Ankyloglossia; bilobed tongue	Buccal frenula; small tongue	Redundant sublingual tissue; absent small tongue; tongue cysts	Cleft palate; small tongue	Cleft palate; lobed tongue; lingual hamartomas	Cleft palate; accessory frenulum
Facial	Median pucker of upper lip	Metopic ridge/ trigonocephaly; anteverted nares; upper lip pucker	Hypertelorism	Anteverted nares	Ptosis; cleft lip; micrognathia	Hypertelorism; bifid nasal tip; midline cleft lip	Cleft lip; microstomia; micrognathia	Broad nasal bridge; short nose; median cleft lip
Hand	Postaxial polydactyly	Postaxial polydactyly; clinodactyly	Duplicated thumb; central polydactyly	Postaxial polydactyly	Postaxial polydactyly	Postaxial polydactyly; bifid thumb	Pre- and postaxial polydactyly	Postaxial polydactyly (occasional)
Foot	Postaxial polydactyly	Postaxial polydactyly	Duplicated great toe	Postaxial polydactyly; broad or bifid great toe	Polydactyly	Pre-and postaxial polydactyly	Clubfoot	
Skeletal	Short limbs; fibula shorter than tibia	Short limbs	Mesomelic shortness	Short limbs	Bowed tibiae	Proximal tibial hypoplasia	Bell-shaped thorax; short-bowed tibia	Short ribs; bowed long bones; fibula shorter than tibia; small scapula & ilia
Heart defects	Atrial and septal defects	Variable	Occasional	Complex	Variable	Variable	Occasional	Occasional
Kidney defects		Various defects	Hydronephrosis; renal dysplasia	Hypoplasia; horseshoe	Renal agenesis; renal cysts		Renal cysts	Dysplasia
Brain anomalies	Dandy-Walker	Cerebellar vermis hypoplasia	Cerebellar atrophy	Hypothalamic hamartoma; Dandy-Walker	Agenesis of corpus callosum; cerebellar defects	Agenesis of corpus callosum; holoprosencephaly; cerebellar anomalies; hydrocephalus	Cerebral atrophy; holoprosencephaly encephalocele	Dandy-Walker
Other	Genital anomalies; hypoplastic nails	Anal and genital defects	Genital hypoplasia	Absent epiglottis; anal and genital defects	Genital defects; other visceral defects	Various other defects	Anal atresia; genital defects; lung hypoplasia	Genital defects; GI anomalies
Inheritance	AR	AR	AR or AD	AD	AR	AR	AR	AR

axial polydactyly, but did not have epiglottal anomalies or preaxial polydactyly. One child in the sibship also had cardiac and renal defects. Nevin and Thomas [1989] also described a boy with a diagnosis of OFDS IV. That child had short humeri, radii and ulnae, a cardiac defect, and laryngeal/epiglottal anomalies.Three years later, they described an affected paternal second cousin with a similar phenotype, but no cardiac defect. These patients most resemble our patients 4 and 5 and likely represent a distinct OFDS with autosomal recessive inheritance (Table II). What distinguishes these patients from those considered to have "classic" OFDS IV is that they have greater skeletal involvement, abnormalities of the epiglottis and/or trachea and reduced survival.

Additional patients stated to have Mohr-Majewski "compound," or OFDS IV, include those described by Meinecke and Hayek [1990], Gillerot and Koulischer [1988], Ades et al. [1994], and Silengo et al. [1987]. The patients of the first three reports had tibial defects; those of the fourth did not. Since the patient described by Silengo et al. [1987] also had central polydactyly and mental retardation, a better diagnosis may be OFDS VI (Varadi syndrome), as also suggested by Muenke et al. [1990]. The children with tibial defects all had an essentially lethal condition. Multiple visceral anomalies were present in all three and included laryngeal, cardiac, genital, renal, and cerebral anomalies in two or more of the patients (Table III). Although there are similarities to patients listed in Table II, none of them had short arms, so for the time being distinction between the two groups is being made.

It is tempting to diagnose any child with oral, facial, and digital anomalies with tibial defects as having OFDS IV syndrome. An important condition to consider in the differential diagnosis is OFDS VIII [Edwards et al., 1988]. This is an X-linked recessive OFD syndrome comprising laryngeal anomalies and shortness of long bones, in addition to facial, oral, and digital (polydactyly of hands and feet) anomalies.

There are several other syndromes that include anomalies of these same systems [Toriello, 1988, 1993]. Among those are the Robinow [1993], Ellis van Creveld [Gorlin et al., 1990], Optiz C [de Koster et al., 1990; Reynolds et al., 1990; Cleper et al., 1993], Pallister-Hall [Clarren et al., 1980; Finnigan et al., 1991], Smith-Lemli-Opitz II [Curry et al., 1987; Gorlin et al., 1990], hydrolethalus [Aughton and Cassidy, 1987], Meckel [Salonen, 1984], and Beemer-Langer [Lim et al., 1991; Yang et al., 1991] syndromes (Table IV). Neri et al. [1995] recently reviewed the OFDS, short-rib polydactyly syndromes (SRPS), and related conditions (Pallister-Hall, hydrolethalus, and Kaufman-McKusick syndromes) and emphasized the marked phenotypic overlap among these conditions. He suggested the designation oral-facial-skeletal syndromes for all the above entities and also suggested they formed a community of syndromes. To that end, the children described in Tables II and III would all fall within that spectrum.

Given this complex group of conditions, what is the purpose of attempts at classification? Although many of these conditions are autosomal recessive, such as classic OFDS IV and the OFDS described by Chitayat et al. [1992] and present in our patients 4 and 5, OFDS VIII is X-linked recessive, Pallister-Hall syndrome is likely autosomal dominant [Donnai, 1993], and the "lethal" OFDS in Table III has an unknown mode of inheritance (although parents were consanguineous in the report of Ades et al., 1994). Thus an accurate diagnosis is essential for precise appraisal of recurrence risks. In addition, among the autosomal recessive entities, there is a vast difference in prognosis. Some children with true OFDS IV either had normal mental development or mild delay; in contrast, other children also described as having OFDS IV had a lethal outcome. The distinction is therefore important for providing accurate prognosis for families. Finally, understanding of the molecular basis of the OFDS can be better achieved if precise delineation of this group of conditions exists. Although the suggestions that many of these phenotypes are the result of compound heterozygosity [Neri et al., 1995] are intriguing, we would argue that in some instances a child with a transitional phenotype (and thus a candidate for having compound heterozygosity) who is the product of a consanguineous mating [e.g., the patient of Franceschini et al., 1995] would be more likely to be homozygous for the same mutation, rather than have different alleles of the same gene. Finally, although the comparison to the Apert/Crouzon situation is also intriguing [Neri et al., 1995], it is unlikely that autosomal recessive disorders will demonstrate a similar phenomenon. Therefore, care must be taken to avoid premature lumping, lest possible etiological clues be missed.

However, until the molecular basis for these syndromes is understood, what should one do with the "unclassifiable" patient, such as our patient 1? Although the combination of oral, facial, and digital anomalies with limb defects suggests the presence of OFDS IV, it is more appropriate to suggest that the diagnosis remains unknown and the recurrence risk may be 25%.

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